Endovascular Treatment Accounts for a Change in Brain Arteriovenous Malformation Natural History Risk

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Summary

This study estimated the risk and rates of intracranial hemorrhage (ICH) in patients harboring brain arteriovenous malformation (BAVM) after endovascular embolization. One hundred and forty-four consecutive patients with BAVM treated with endovascular embolization between 1998 and 2003 were retrospectively reviewed. The risk of ICH subsequent to endovascular embolization was studied using Kaplan-Meier curves.

We reviewed 144 patients with BAVM treated with endovascular embolization. Two hundred and sixty-nine procedures were performed, 69 were performed with silk sutures, 18 with coils, 137 with NBCA and 36 with Onyx18. Twenty-three (16.0%) patients were treated with additional gamma-knife radiosurgery and one (0.7%) with additional surgical AVM excision. Complete obliteration of BAVMs was achieved in 20 patients (13.9%). During a mean follow-up of 5.9 years for the ICH group and 6.9 years for the non-ICH group, hemorrhages occurred in 11 (17.7%) of the ICH patients and in nine (11%) of the non-ICH group (p>0.1). The annual risk of hemorrhage was 3.0% and 1.6%, respectively. In the multivariate regression model, the adjusted relative risk (RR) for hemorrhage at initial presentation was 1.6 (95% CI 1.2-3.2; p>0.1). Deep venous drainage, male sex, age or AVM size were not significantly associated with subsequent hemorrhage. ICH and non-ICH groups did not differ in progression to subsequent ICH after endovascular embolization (log-rank X^2=1.339, p>0.1) in survival analyses. The overall annual hemorrhage risk for all patients after endovascular embolization was 2.1%.

Endovascular embolization alone or combined with gamma-knife radiosurgery or surgical treatment are able to decrease ICH occurrence compared to abstention.

Introduction

Brain arteriovenous malformations (BAVMs) are a major cause of hemorrhagic stroke in young adults [1-4]. Treatment decisions can be challenging because of complex angioarchitecture involving eloquent brain areas and a relative lack of unbiased natural history data [5-8]. Accurate estimates for risk and rates of ICH subsequent to embolization of BAVM are needed to provide a quantative basis for evaluating interventional strategies to help guide practice management. A primary unresolved issue is whether endovascular embolization decreases the risk of subsequent hemorrhage or does not affect future bleeding risk [9]. Our hypothesis was that BAVM embolization is associated with a low complication rate and a lower rate of subsequent ICH in the clinical course. We present data obtained from a single center, compared with earlier reports. These heterogeneous data confirm earlier reports and make it possible to carefully balance the risks of intervention with endovascular management.

Patients and Methods

This study was based on retrospective enrolment between 1998 and 2003, of consecutive 164 patients with BAVM. We also excluded pa-

tients with insufficient baseline or follow-up information (20 patients from a total of 164, leaving 144 for analysis). The patient clinical records and the angiographic images were reviewed by one or more of the study physicians to determine or confirm the underlying diagnosis. A standardized definition was used as previously described: an abnormal tangle of vessels that results in arteriovenous shunting, excluding vein of Galen AVM, cavernous malformations, anomalous venous drainage, ruptured arterial aneurysms, dural arteriovenous fistulae, venous malformations, venous varices, or any of the other rare types of cerebrovascular anomalies. The diagnosis of BAVM was based on information from conventional digital subtracted angiography.

Ten AVMs were located an infratentorial location and 134 were supratentorial. Sixty-two patients (43.1%) initially presented with hemorrhage, defined as a clinically symptomatic event (sudden onset headache, seizure, focal deficit, or a combination of these features) with signs of fresh bleeding on computed tomography or magnetic resonance brain imaging (hemorrhage group). The same criteria were used for the diagnosis of hemorrhage during the follow-up period. The remaining 82 patients (56.9%) initially presented with symptoms or signs unrelated to hemorrhage (table 1) and served as the comparison group (non-hemorrhage group). The time between presentation and endovascular treatment was two to nine days (mean, 5.8 days). Patients with one or more hemorrhages after initial presentation were censored at the first hemorrhage event.

The primary goal of endovascular treatment was to achieve reduction of risk for future bleed and was to achieve a cure in AVMs of small size. Superselective microcatheter was cannulated of arteries feeding the AVM and coils, silk suture, N-butyl cyanoacrylate or Onyx18 were used to occlude the fistulae. Onyx was used in an effort to achieve cure, silk achieved a proximal occlusion which was of benefit pre surgery and NBCA was good for targeted occlusion. The technique remained the same throughout the study period. Sixty-six patients were embolized with one session each; 44 patients were embolized with two sessions

Table 1 **Baseline characteristics and initial presentation in 144 consecutive patients with cerebral AVM treated endovascularly**

	Haemorrhage group (n=62)	**Non-haemorrhage group (n=82)**	**Total (n=144)**
Initial AVM presentation			
Haemorrhage	62(100%)	–	62 (43.1%)
Seizure	–	42(51.2%)	42(29.2%)
Headaches	–	25 (30.5%)	25(17.4%)
Focal deficit	–	12(14.6%)	12(8.3%)
No symptoms	–	3(3.7%)	3(2.1%)
Demography			
Mean (SD) age in years	26.1(11.2)	29.3(12.5)	27.9(12·0)
Male	36(58.1%)	56(68.3%)	92(63.9%)
Female	26(41.9%)	26(31.7)	52(36.1%)
AVM characteristics			
Small size	15(24.2%)	6(7.3%)	21(14.6%)
Deep drainage	20(32.3%)	5(6.1%)	25(17.4%)
Infratentorial location	6(9.7%)	4(4.9%)	10(69.4%)
Follow-up			
Total follow-up time	364.5y	566.8y	931.3y
Median time to event*	7.3y	3.5y	–
ICH after embolization	11(17.7%)	9(11.0%)	20(13.9%)

** By Stein and Kader9 criteria: small AVM=maximum diameter 2·5 cm.*
ICH rates and standard errors estimated from Kaplan-Meier survival analysis.
** Median time to event describe time to haemorrhage among those patients with haemorrhage in each respective group.*

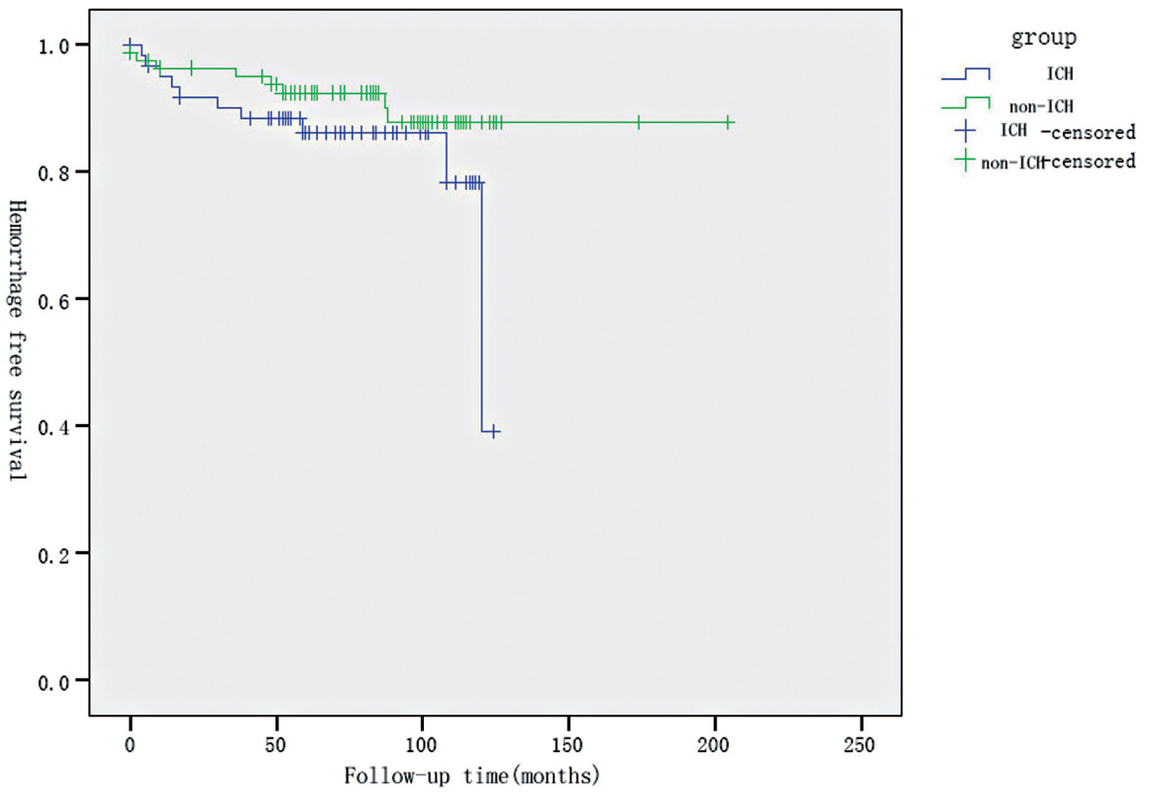

Figure 1 Kaplan-Meier survival analysis of hemorrhage during follow-up after endovascular treatment according to initial presentation.

each; 24 patients were embolized with three sessions each; six were embolized with four sessions each and two were embolized with five sessions. Two hundred and sixty procedures were performed, 69 were performed with silk sutures, 18 with coils, 137 with NBCA and 36 with Onyx18.

Follow-up was from two months to 11 years (median 6.75 years; mean 6.5 years) after the first embolization procedure. The frequency of AVM hemorrhage in the two groups during follow-up was displayed using Kaplan-Meier curves. Differences between hemorrhage-free survival for patients who presented with and without ICH were analyzed using the log rank test. A further multivariate proportional-hazards regression model (including AVM size and drainage, as well as the patient's age and sex, and initial hemorrhage) tested the effect of these factors. AVM size definition followed the generally accepted Stein and Kader classification [16] (Table 1). Patients whose angiograms showed venous AVM drainage exclusively through the periventricular, Galenic or cerebellar pathways were classified as having deep-venous drainage. The study was reviewed and approved by the ethics committee of the Beijing Tiantan Hospital.

Results

Among 144 BAVM patients identified, 62 (43.1%) presented with an ICH. Using a hierarchical system, the remaining presentations were 42 (29.2%) with seizure, 25 (17.4%) with headaches, and 12 (8.3%) with focal deficits. Three were incidental ones not definitively attributable to the BAVM (Table 1). Two hundred and sixty-nine procedures were performed, 69 were performed with silk sutures, 18 with coils, 137 with NBCA and 36 with Onyx18. Sixty-six patients were embolized with one session each; 44 patients were embolized with two sessions each; 24 patients were embolized with three sessions each; six were embolized with four sessions each and two were embolized with five sessions. Complete obliteration of BAVMs was achieved in 20 patients (13.9%). Three aneurysms on AVM feeding arteries

Table 2 **Results of multivariate regression model**

	Relative risk	(95%CI)	X^2	P
ICH before treatment	1.7	(1.1-3.2)	1.5	>0.05
Age≤30	2.2	(1.5-2.3)	1.3	>0.1
Male sex	0.8	(0.6-0.9)	1.9	>0.05
Small AVM size	0.7	(0. 2-2.1)	0.4	>0.5
Deep drainage	1.2	(0.4-3.7)	0.11	>0.5

were coiled. Complications occurred in 11 patients, three ICHs which caused one death; six transient neurological deficits and one persistent neurological deficit. Twenty-three (16.0%) patients were treated with additional gamma-knife radiosurgery and one (0.7%) with additional surgical AVM excision. Two gamma-knife radiosurgery and one surgical excision were performed after subsequent ICH. The mean follow-up time was 5.9 years (range 0-10.3years) in the hemorrhage group and 6·9 years (0-11 years) in the non-hemorrhage group. In the group that presented with ICH, 11 (17.7%) had a subsequent ICH after treatment, the median time to hemorrhage was 7.3 years. Among patients who presented without ICH, nine (11.0%) had a subsequent ICH, and the median time to hemorrhage was 3.5 years. The annual rate of bleeding after AVM embolization was 3.0% in the ICH group and 1.6% in the non-ICH group. The annual rate of bleeding was higher for the first year (6.5%) than in subsequent years (2.3%) in the hemorrhage group. By contrast, in the non-hemorrhage group, the rate was 4.9% for the first year and 1% for subsequent years. Hemorrhage during follow-up was not significantly associated with hemorrhage at initial presentation was 1.6 (95% CI 1.2–3.2; p>0.1) (Table 2). Deep venous drainage, male sex, age (≤30 years) or AVM size were not significantly associated with subsequent hemorrhage. The regression model also showed no significant effect was found for initial presentation with seizure (RR, 0.8, X^2=0.008]), focal deficit (RR,0), or headache (0.84, X^2=0.090) (Table 2). ICH and non-ICH groups did not differ in progression to subsequent ICH after endovascular embolization (log-rank X^2=1.339, p>0.1) in survival analyses (Figure 1). The overall annual hemorrhage risk for all patients after endovascular embolization was 2.1%. Actuarial estimate of the cumulative ten-year risk of hemorrhage after AVM embolization was 14% (SE 6.6), and 17.8% (SE 11.5) in the ICH group and 11% (SE 7.6) in the non-ICH group. The comparison of the rates of hemorrhage in the two groups after year one (6.5 vs 3.0%) lacked statistical power, but gave a relative risk of 2.17 (X^2=0.165; p>0.1). Follow-up hemorrhages were exclusively intraventricular in one (5%) patient, intraparenchymatous in ten (50%), subarachnoidal in one (5%), combined intraparenchymatous and intraventricular in eight (40%).

Two patients without any neurological deficit had an exclusively intraventricular or subarachnoid hemorrhage. Similarly, a focal neurological deficit related to the initial presentation hemorrhage was found in only 19 (30.6%) of the 62 ICH-group patients; a disabling deficit was seen in only six (9.8%) cases, gave a relative risk of 1.27 (X^2=0.47; p>0.1). For eight (40%) of the 20 patients with an AVM hemorrhage during follow-up, no associated neurological deficit was found. Among the eight with deficits, these were non-disabling or mildly disabling (Rankin scale scores <3) in seven. The other one had disabling deficits (Rankin scale scores 3). There were four (2.8%) deaths due to AVM ICH within one year after embolization: at two months, five months, nine months and 12 months after an embolization that had partially obliterated an AVM: three in the non-ICH group and one in the ICH group.

Discussion

To investigate whether endovascular treatment could account for a possible change in natural history risk, we undertook a study based on a consecutive series of patients diagnosed by BAVMs, which were all treated with endovascular embolization. Pooled data for 160 reported AVM cases suggested that roughly 60% present with hemorrhage [10]. In the few estimates available, the rate of hemorrhage in the

course of untreated AVM was between 2% and 4% per year [10]. A higher rate has been reported for patients initially presenting with hemorrhage than for patients with other diagnostic symptoms [11,12]. Compared with previous studies, the first year bleeding rate was lower (6.5% vs 9.65% to 32.9%) for the first year in the hemorrhage group [11-13], whereas in the non-hemorrhage group the rate was slightly higher (4.9% vs 0% to 3.6%) for the first year as a result of treatment [11-13]. Our study shows a significantly lower risk of subsequent hemorrhage at the first year for AVM patients who initially present with hemorrhage. In untreated BAVMs, the effect of initial presentation with hemorrhage remained significant in the regression model that included age, sex, small AVM size, and deep drainage [12,14-17]. But after embolization, no significant association with hemorrhage during follow-up was found for initial presentation, male sex and exclusively deep-venous drainage.

Current clinical practice assumes a steady uniform long-term risk of AVM bleeding [2,18-21], but there are no observations to justify this notion. Our finding of a declining risk of hemorrhage over time in patients with and without hemorrhage at initial presentation may support the hypothesis of an improvement of the long-term risk of AVM hemorrhage. On the other hand, a 9.65% to 32.9% first year rate of hemorrhage alone may well be viewed as a substantial risk, justifying a plan of embolization targeted towards high risk bleeding angioarchitecture features such as false aneurysms [11-13,22]. In the non-ICH group, a 4.9% first year rate of hemorrhage should be viewed as a substantial risk after endovascular treatment while with a low risk in the following years. In our series, the ICH rate related to embolization procedure was 0.7% (2/269) with a 2.2% (6/269) rate of transient ischemic complication and a 0.4% (1/269) rate of persistent ischemic complication.

Our data come from the largest neurosurgical center of China and this is a heterogeneous population. Thus, we believe that our sample is representative of the general AVM population. But a selection bias may have been introduced by choice of patients deemed endovascular treatment, thereby shifting cases with large and deeply located AVMs in eloquent brain areas into our sample. Because of the available treatment options and current concerns about serious outcomes from hemorrhage, prospective natural-course studies in unselected samples of patients with AVM will continue to be difficult [23-25].

Conclusions

Endovascular embolization was necessary for ruptured BAVMs because it decreases the ICH risk in the subsequent period. Although endovascular embolization was associated with worse outcome for unruptured AVMs within the first year after treatment, the subsequent ICH risk was also decreased. The ICH related to endovascular embolization was low.

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